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(54) Aminomethyl oxooxazolidinyl aroylbenzene derivatives useful as antibacterial agents.

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FR-A- 2 500 450
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EP 0 312 000 B1

Description

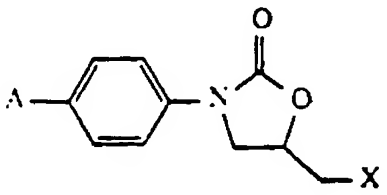
Technical Field

This invention relates to novel aminomethyl oxooxazolidinyl aroylbenzene derivatives, their preparation, to pharmaceutical compositions containing them, and to methods of using them to alleviate bacterial infections.

Background of the Invention

At the present time, no existing antibacterial product provides all features deemed advantageous. There is continual development of resistance by bacterial strains. A reduction of allergic reactions and of irritation at the site of injection, and greater biological half-life (i.e., longer in vivo activity) are currently desirable features for antibacterial products.

U.S. Patent 4,128,654 issued to Fugitt et al. on December 5, 1978, discloses, among others, compounds of the formula:

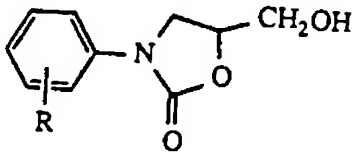


where

A = $RS(O)_n$;
X = Cl, Br or F;
R = C_1-C_3 alkyl; and
n = 0, 1 or 2.

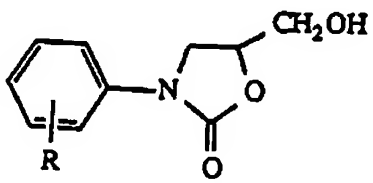
The compounds are disclosed as being useful in controlling fungal and bacterial diseases of plants.

U.S. Reissue Patent 29,607 reissued April 11, 1978 discloses derivatives of 5-hydroxymethyl-3-substituted-2-oxazolidinones of the formula:



where R is H, F, CH_3, or CF_3. Such compounds are described as having antidepressive, tranquilizing, sedative, and antiinflammatory properties.

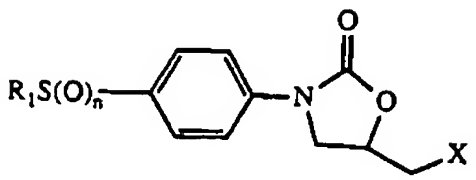
U.S. Patent 4,250,318, which was issued on February 10, 1981, discloses antidepressant compounds of the formula:



where R can be, among others, a para-n-pentylamino group, and SR_1 group where R_1 is C_1-C_5 alkyl, or an

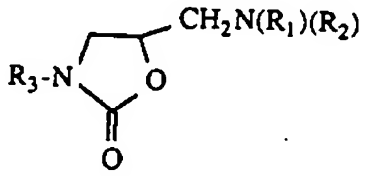
acetylmethylthio group.

U.S. Patent 4,340,606 issued to Fugitt et al. on July 20, 1982, discloses antibacterial agents of the general formula:



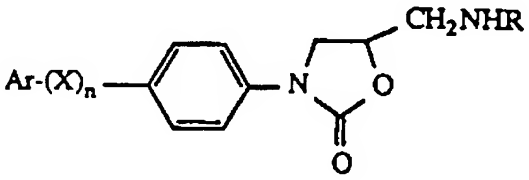
where
R_1 = CH_3, C_2H_5, CF_2H, CF_3 or
CF_2CF_2H; and
X = OR_2 (R_2 = H or various acyl moieties).

U.S. Patent 3,687,965, issued to Fauran et al. on August 29, 1972, discloses compounds of the formula:



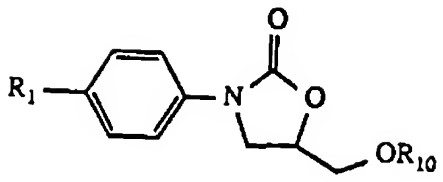
where
$-N(R_1)(R_2)$ represents either dialkylamino radical in which the alkyl portions have one to five carbon atoms, or a heterocyclic amino radical which may be substituted by an alkyl radical having one to five carbon atoms or by a pyrrolidinocarbonylmethyl radical, and
R_3 represents a phenyl radical which may be substituted by one or more of the following radicals:
an alkoxy radical having one to five carbon atoms;
a halogen atom;
a trifluoromethyl radical, or
a carboxyl radical which may be esterified.
The patent states that these compounds possess hypotensive, vasodilatatory, spasmolytic, sedative, myorelaxant, analgesic and antiinflammatory properties. There is no mention of antibacterial properties.

Belgian Patent 892,270, published August 25, 1982, discloses monoamine oxidase inhibitors of the formula

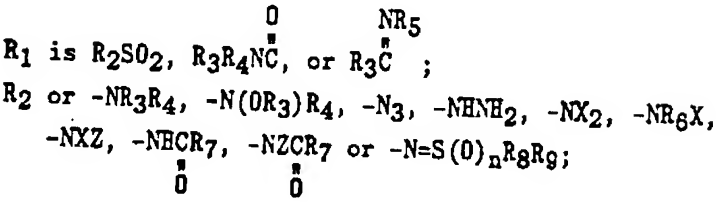


where
R is H, C_1-C_4 alkyl or propargyl;
Ar is phenyl, optionally substituted by halo or trifluoromethyl;
n is 0 or 1; and
X is $-CH_2CH_2-$, $-CH=CH-$, an acetylene group or $-CH_2O-$.

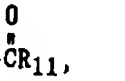
U.S. Patent 4,461,773 issued to W. A. Gregory on July 24, 1984, discloses antibacterial agents of the formula

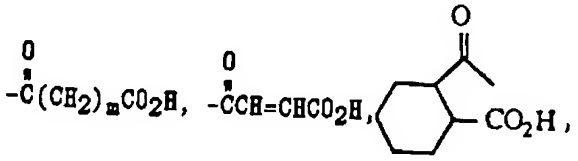


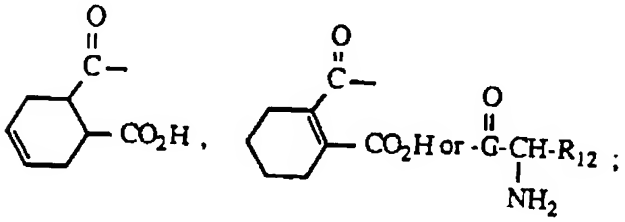
wherein, for the *l*, and mixtures of the d and *l* stereoisomersof the compound,



R_3 and R_4 are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;
R_5 is NR_3R_4 or OR_3;
R_6 is alkyl of 1-4 carbons;
R_7 is alkyl of 1-4 carbons, optionally substituted with one or more halogens;
R_8 and R_9 are independently alkyl of 1-4 carbons or, taken together are $-(CH_2)_p-$;
R_{10} is H, alkyl of 1-3 carbons,



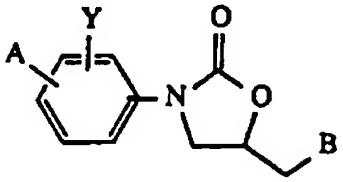




R_{11} is alkyl of 1-12 carbons;
R_{12} is H, alkyl of 1-5 carbons, CH_2OH or CH_2SH;
X is Cl, Br or I;
Z is a physiologically acceptable cation;
m is 2 or 3;
n is 0 or 1; and
p is 3, 4 or 5;
and when R_{10} is alkyl of 1-3 carbons, R_1 can also be $CH_3S(O)_q$ where q is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

European Patent Application 127,902, published December 12, 1984, and 184,170, published June 11, 1986, disclose antibacterial agents of the formula:



wherein, for the *l*, and mixtures of the d and *l* stereoisomersof the compound,

A is $-NO_2$, $-S(O)_nR_1$, $-S(O)_2-N=S(O)_pR_2R_3$, $-SH$,

$-SCR_4$, $-COR_{23}$, $-COR_{25}$, $-CONR_5R_6$, $-\overset{NR_7}{\overset{\|}{C}}-R_{23}$,

$-\overset{OR_8}{\underset{R_6}{\overset{|}{\underset{|}{C}}}}-R_{23}$, $-\overset{OR_8}{\underset{R_6}{\overset{|}{\underset{|}{C}}}}-R_{25}$, $-\overset{O\overset{\|}{C}R_8}{\underset{R_6}{\overset{|}{\underset{|}{C}}}}-R_{23}$, $-\overset{O\overset{\|}{C}R_8}{\underset{R_6}{\overset{|}{\underset{|}{C}}}}-R_{25}$, CN, $-OR_5$

halogen, $-NR_5R_6$, $-\overset{R_5}{\overset{|}{N}}COR_4$, $\overset{R_5}{\overset{|}{N}}S(O)_nR_4$,

$CR_{23}(OR_{16})OR_{17}$, $-\overset{NR_5R_6}{\overset{|}{\underset{R_9}{\underset{|}{CR_{23}}}}}$, alkyl

of 1 to 8 carbons, optionally substituted with one or more halogen atoms, OH, =O other than at alpha position, $S(O)_nR_{24}$, NR_5R_6, alkenyl of 2-5 carbons, alkynyl of 2-5 carbons or cycloalkyl of 3-8 carbons;
R_1 is C_1-C_4 alkyl, optionally substituted with one or more halogen atoms, OH, CN, NR_5R_6 or

CO_2R_8; C_2-C_4 alkenyl; $-NR_9R_{10}$; $-N_3$; $-NH\overset{O}{\overset{\|}{C}}R_4$

$-NZ\overset{O}{\overset{\|}{C}}R_4$; $-NX_2$; $-NR_9X$; $-^-NXZ^+$;

R_2 and R_3 are independently C_1-C_2 alkyl or, taken together are $-(CH_2)_q-$;
R_4 is alkyl of 1-4 carbons, optionally substituted with one or more halogens;
R_5 and R_6 are independently H, alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;

R_7 is $-NR_5R_6$, $-OR_5$ or $NHCR_5$ (O);

R_8 is H or alkyl of 1-4 carbons;
R_9 is H, C_1-C_4 alkyl or C_3-C_8 cycloalkyl;
R_{10} is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_3-C_4 cycloalkyl, $-OR_8$ or $-NR_{11}R_{11A}$;
R_{11} and R_{11A} are independently H or C_1-C_4 alkyl, or taken together, are $-(CH_2)_r-$;
X is Cl, Br or I;
Y is H, F, Cl, Br, alkyl or 1-3 carbons, or NO_2, or A and Y taken together can be $-O-(CH_2)_tO-$;
Z is a physiologically acceptable cation;
n is 0, 1 or 2;
p is 0 or 1;
q is 3, 4 or 5;
r is 4 or 5;
t is 1, 2 or 3;

B is $-NH_2$, $-N(R_{12})-C(O)-R_{13}$, $-N(R_{12})-S(O)_uR_{14}$, or N_3;

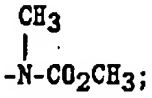
R_{12} is H, C_1-C_{10} alkyl or C_3-C_8 cycloalkyl;
R_{13} is H; C_1-C_4 alkyl optionally substituted with one or more halogen atoms; C_2-C_4 alkenyl; C_3-C_4 cycloalkyl; phenyl; $-CH_2OR_{15}$; $-CH(OR_{16})OR_{17}$;

$-CH_2S(O)_vR_{14}$; CR_{15}(O); $-OR_{18}$; $-SR_{14}$; $-CH_2N_3$;

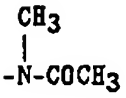
aminoalkyl groups derived from α-amino acids such as glycine, L-alanine, L-cysteine, L-proline, and D-alanine; $-NR_{19}R_{20}$; or
$C(NH_2)R_{21}R_{22}$;
R_{14} is C_1-C_4 alkyl, optionally substituted with one or more halogen atoms;
R_{15} is H or C_1-C_4 alkyl, optionally substituted with one or more halogen atoms;
R_{16} and R_{17} are independently C_1-C_4 alkyl or, taken together, are $-(CH_2)_m-$;
R_{18} is C_1-C_4 alkyl or C_7-C_{11} aralkyl;
R_{19} and R_{20} are independently H or C_1-C_2 alkyl;
R_{21} and R_{22} are independently H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl or, taken together, are $-(CH_2)_s-$;
u is 1 or 2;
v is 0, 1 or 2;
m is 2 or 3;
s is 2, 3, 4 or 5; and
R_{23} is H, alkyl of 1-8 carbons optionally substituted with one or more halogens, or cycloalkyl of 3-8 carbons;
R_{24} is alkyl of 1-4 carbons or cycloalkyl of 3-8 carbons;
R_{25} is alkyl of 1-4 carbons substituted with one or more of

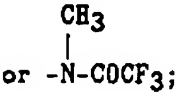
$-S(O)_nR_{24}$, $-OR_8$, $-OCR_8$ (O), $-NR_5R_6$, or

alkenyl of 2-5 carbons optionally substituted with CHO; or a pharmaceutically suitable salt thereof; provided that:
1) when A is CH_3S-, then B is not

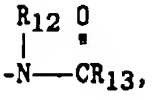


2) when A is CH_3SO_2-, then B is not





3) when A is H_2NSO_2- and B is

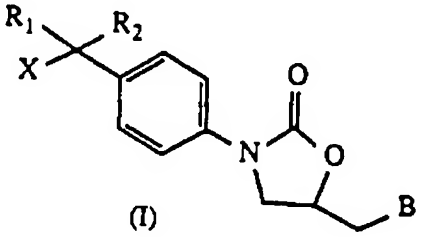


then R_{12} is H;
4) when A is -CN, B is not $-N_3$;
5) when A is $(CH_3)_2CH$, B is not $NHCOCH_2Cl$;
6) when A is OR_5, then B is not NH_2;
7) when A is F, then B is not $NHCO_2CH_3$.

None of the above-mentioned references suggest the novel antibacterial compounds of this invention.

Summary of the Invention

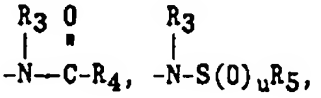
According to the present invention, there is provided an oxazolidinone having the formula:



(I)

where for the *t* isomer or racemic mixtures containing it

B is NH_2,



or N_3

u is 1 or 2;

R_3 is H, alkyl of 1-10 carbon atoms, or cycloalkyl of 3-8 carbon atoms;

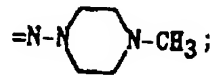
R_4 is H, alkyl of 1-4 carbon atoms, alkenyl of 2-4 carbon atoms, cycloalkyl of 3-4 carbon atoms, or OR_5;

R_5 is alkyl of 1-4 carbon atoms;

R_1 and R_2 taken together are H_2, H and OH, =O, =NOH, H and $N(R_6)_2$, $=NOR_5$,

$$=NOCR_4$$

or



R_6 is H or alkyl of 1-4 carbon atoms;

X is pyridinyl or phenyl optionally substituted with from 1-3 substituents each independently selected from a group selected from halogen, alkyl of 1-4 carbon atoms, NO_2, OR_5, or $S(O)_mR_5$; and

m is 0, 1 or 2;

or a pharmaceutically suitable salt thereof.

Also provided is a process for preparing compounds of Formula (I), such a process being described in detail hereinafter.

Additionally provided are a pharmaceutical composition containing a compound of Formula (I) and a method of using a compound of Formula (I) to treat a bacterial infection in a mammal.

Preferred Embodiments

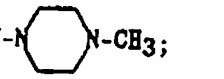
Preferred compounds are the oxazolidinones of Formula (I) wherein:

(a) B is

$$-NHCR_4;$$

where R_4 is H, CH_3, or OR_5; or

(b) R_1 and R_2 taken together are H_2, H and OH,

=O, =NOH, or 

or

(c) X is 3-pyridinyl or phenyl optionally substituted with from 1-2 substituents each independently selected from halogen, NO_2, $S(O)_mR_5$ or OR_5.

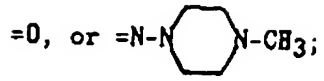
More preferred compounds are the oxazolidinones of Formula (I) wherein:

(a) B is

$$-NHCCH_3;$$

or

(b) R_1 and R_2 taken together are H_2, H and OH,



or

(c) X is phenyl optionally substituted with from 1-2 substituents each selected from F, Cl, NO_2, or OCH_3.

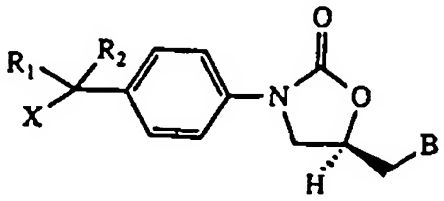
Specifically preferred are the following compounds:

- (ℓ)-N-[3-[4-(2,4-difluorobenzoyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(4-nitrobenzoyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide;
- (ℓ)-N-[3-[4-(4-fluorobenzoyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

Detailed Description

The compounds of Formula (I) contain at least one chiral center and, as such, exist as two individual isomers or as a mixture of both. This invention relates to the levorotatory isomer (ℓ), which for many of the compounds in this invention can be referred to as the (S) isomer, as well as mixtures containing both the (R) and (S) isomers. Additional chiral centers may be present in the B group, or when R_1 and R_2 taken together are H and OH or H and $N(R_6)_2$. The invention relates to all possible stereoisomers of the above.

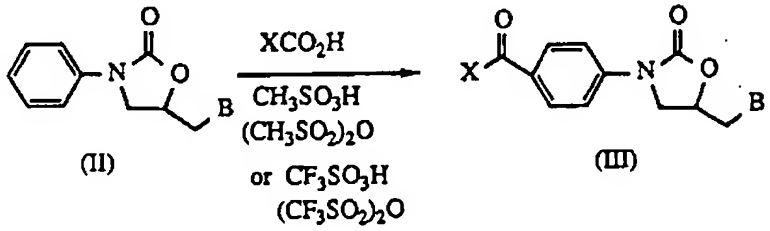
For the purposes of this invention, the ℓ-isomer of compounds of Formula (I) is intended to mean compounds of the configuration depicted; when B is NHAc, and closely related groups, this isomer is described as the (S)-isomer in the Cahn-Ingold-Prelog nomenclature:



Synthesis

Compounds of Formula (I) where R_1 and R_2 taken together are =O, and X and B are as previously defined can be prepared as follows:

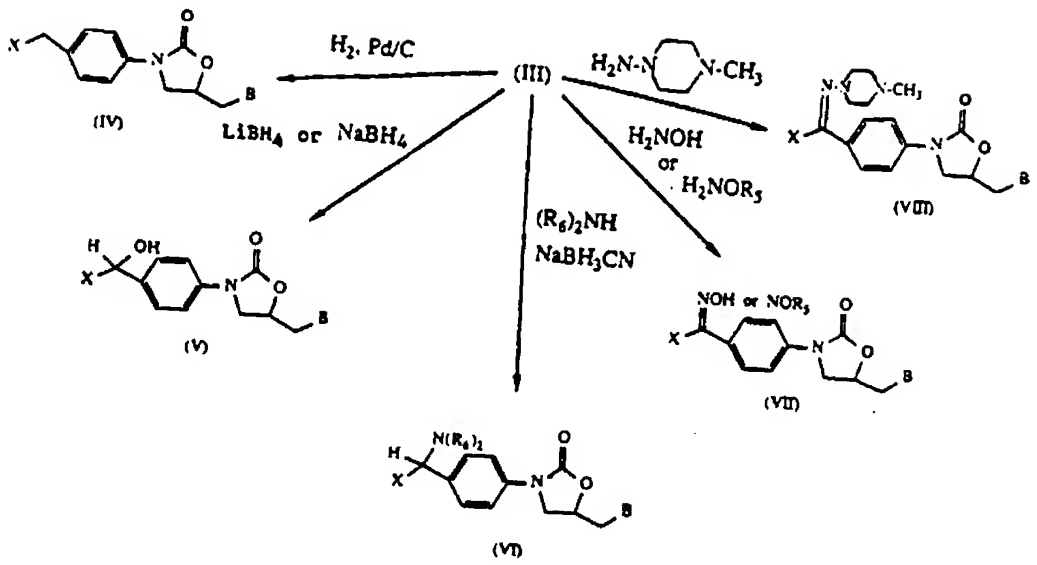
Scheme 1



Compounds of Formula (II), which are prepared by the process previously described in published European applications 127,902 and 184,170, are converted to aroyl derivatives (III) by treatment of either a mixture of methanesulfonic acid and methanesulfonic anhydride or a mixture of trifluoromethanesulfonic acid and trifluoromethanesulfonic anhydride and the corresponding aroyl carboxylic acid at room temperature to 80°C.

Compounds of Formula (I) where R_1 and R_2 taken together are not =O but as described previously can be prepared as follows:

Scheme 2



Aroyl derivatives (III) can be converted to compounds (IV)-(VIII) by standard procedures. Hydrogenation of (III) in a solvent such as ethyl acetate, methanol, or ethanol in the presence of a hydrogenation catalyst such as Pd/C or Pt/C under 0-15 lb hydrogen pressure at room temperature to 80 °C gives (IV). Alcohols (V) are prepared according to the procedure described in Example 19 by use of an alkali metal borohydride. Reaction of (III) with $(R_6)_2NH$ in an alcoholic solvent such as methanol or ethanol at room temperature to 80 °C in the presence of sodium cyanoborohydride affords amines (VI). Treatment of (III) with hydroxyamine hydrochloride or H_2NOR_5 in the presence of a base such as pyridine or triethylamine in an alcoholic solvent such as methanol or ethanol at room temperature to 100 °C yields oximes (VII). Finally, aroyl derivatives (III) are converted to (VIII) by reacting with 1-amino-4-methylpiperazine in a refluxing solvent such as tetrahydrofuran (THF) or dioxane containing boron trifluoride etherate.

Pharmaceutically suitable salts of compounds of Formula (I) can be prepared in a number of ways known in the art. When R_1, R_2, X or B contain a basic nitrogen, pharmaceutically salts include these resulting from treatment with acids such as acetic, hydrochloric, sulfuric, phosphoric, succinic, fumaric, ascorbic and glutaric acid.

The invention can be further understood by the following examples in which parts and percentages are by weight unless indicated otherwise.

Example 1

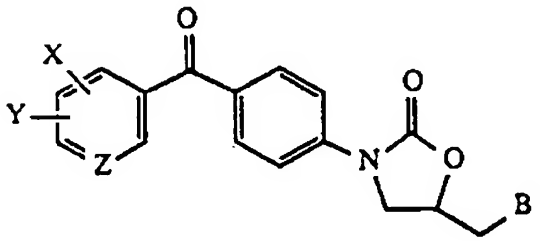
Preparation of (ℓ)-N-[3-[4-(4-fluorobenzoyl)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (I; R_1, R_2=O, X = 4-C_6H_4F, B = $NHCOCH_3$)

To a solution of methanesulfonic anhydride (7.45g, 43 mmol), methanesulfonic acid (14 mL), and (ℓ)-N-(3-phenyl-2-oxo-5-oxazolidin-5-yl-methyl)acetamide (2.0g, 9 mmol) was added 4-fluorobenzoic acid (4.8g, 34 mmol). The mixture was stirred at 50-60 °C overnight and allowed to cool to room temperature before being poured into 120 mL ice/water. The resulting mixture was extracted with a chloroform/2-propanol mixture. The organic extract was washed with saturated sodium bicarbonate, saturated brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by flash chromatography followed by crystallization from ethyl acetate. Recovered 2.2g (73%) of the title compound, m.p. 168.5 °-170.5 °C. IR (KBr): 1752, 1652, 1600 cm^{-1}; NMR (d_6-DMSO) δ: 8.29 (m,1H), 7.78 (m,6H), 7.40 (m,2H), 4.79 (m,1H), 4.20 (dd,J = 8,9 Hz,1H), 3.83 (dd,J = 6.5, 9.1 Hz,1H) 3.45 (m,2H), 1.83 (s,3H); C,H analysis, calcd: C 64.04, H

4.81, F 5.33, N 7.86, found: C 64.12, H 4.82, F 5.37, N 7.90; $[\alpha]_D = -31°$ (c = 1.01, acetone).

By using the procedure described in Example 1, the following compounds in Table I were prepared or can be prepared.

Table I



Ex.	X	Y	Z	B	Isomer	m.p. (°C)
1	4-F	H	CH	$NHCOCH_3$	ℓ	168.5-170.5
2	H	H	CH	$NHCOCH_3$	ℓ	175-177
3	$4-OCH_3$	H	CH	$NHCOCH_3$	ℓ	162-163.5
4	4-Cl	H	CH	$NHCOCH_3$	ℓ	222.5-224
5	3-F	H	CH	$NHCOCH_3$	ℓ	166.5-168
6	2-F	4-F	CH	$NHCOCH_3$	ℓ	169-170
7	$2-OCH_3$	4-Cl	CH	$NHCOCH_3$	ℓ	212-214
8	$4-SCH_3$	H	CH	$NHCOCH_3$	ℓ	
9	$4-NO_2$	H	CH	$NHCOCH_3$	ℓ	220-222
10	$4-SOCH_3$	H	CH	$NHCOCH_3$	ℓ	
11	$4-SO_2CH_3$	H	CH	$NHCOCH_3$	ℓ	
12	H	H	CH	NH_2	ℓ	
13	H	H	CH	N_3	ℓ	
14	H	H	CH	NHCO- 	dℓ	
15	H	H	N	$NHCOCH_3$	ℓ	184-185.5
16	$4-CH_3$	H	CH	$NHSOC_2H_5$	dℓ	
17	$2-C_2H_5$	H	CH	$N(CH_3)SO_2CH_3$	ℓ	
18	H	H	N	$N(C_2H_5)COCH_3$	ℓ	

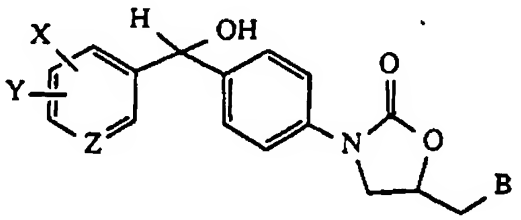
Example 19

Preparation of (ℓ)-N-[3-[4-[(4-fluorophenyl)-(hydroxy)methyl]phenyl]-2-oxooxazolidin-5-yl-methyl]acetamide (I; R_1 = H, R_2 = OH, x = 4-C_6H_4F, B = $NHCOCH_3$)

To a solution of (ℓ)-N-[3-[4-[(4-fluorobenzo)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (1.50 g, 4.2 mmol) in THF (30 mL) was added lithium borohydride (1.05 mL, 2 M in THF, 2.1 mmol). The mixture was stirred at room temperature overnight before quenching with water followed by 1N hydrochloric acid. The solution was diluted with 1N hydrochloric acid and extracted with a chloroform/2-propanol mixture. The organic extract was washed with saturated sodium bicarbonate, saturated brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by flash chromatography. Recovered 0.52 g (34%) of the title compound, m.p. 73-76°C. IR (KBr): 1745,1655 cm^{-1}; NMR (d_6-DMSO) δ: 8.24 (m,1H), 7.41 (m,6H), 7.10 (m,2H), 5.93 (d,J = 4Hz,1H), 5.70 (d,J = 4Hz,1H), 4.69 (m,1H), 4.06 (M,1H), 3.71 (m,1H), 3.39 (m,1H), 1.83 (s,3H); MS: m/z 358.1335 (m^+), calcd. for $C_{19}H_{19}N_2O_4F$, 358.1329; $[\alpha]_D$ = -12° (C = 1.0, ethanol).

By using the procedure described in Example 19, the following compounds in Table II were prepared or can be prepared.

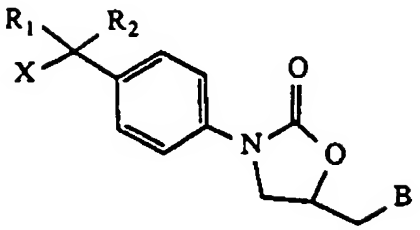
Table II



Ex.	X	Y	Z	B	Isomer	m.p. (°C)
19	4-F	H	CH	$NHCOCH_3$	ℓ	73-76
20	H	H	CH	$NHCOCH_3$	ℓ	68-70
21	2-F	4-F	CH	$NHCOCH_3$	ℓ	70-73
22	4-SCH_3	H	CH	$NHCOCH_3$	ℓ	
23	H	H	CH	$NHCO_2CH_3$	dℓ	
24	4-CH_3	H	CH	$NHSOCH_3$	ℓ	
25	2-C_2H_5	H	CH	$NHSO_2C_4H_9$	ℓ	
26	H	H	N	$NHCOCH_3$	ℓ	
27	4-F	H	CH	N_3	dℓ	
28	H	H	CH	NH_2	ℓ	
29	H	H	CH	$N(CH_3)COC_2H_5$	dℓ	

By using chemistry previously described in Synthesis section, compounds in Table III can be prepared.

Table III



Ex.	X	R_1,R_2	B	Isomer	m.p. (°C)
30	C_6H_5	=N-N(CH)N-CH_3	$NHCOCH_3$	ℓ	
31	4-FC_6H_4	H,NH_2	$NHSOCH_3$	dℓ	
32	4-ClC_6H_4	H,$N(CH_3)_2$	N_3	ℓ	
33	2,4-$F_2C_6H_4$	=NOH	NH_2	ℓ	
34	4-$CH_3C_6H_4$	=NOCH_3	$NHCO_2CH_3$	dℓ	
35	2-pyridyl	=NO$\overset{O}{\overset{\|}{C}}C_2H_5$	NHCO-	ℓ	
36	3-pyridyl	H,NH_2	$N(CH_3)COC_2H_5$	ℓ	
37	4-pyridyl	=N-N(CH)N-CH_3	$N(C_2H_5)SO_2CH_3$	ℓ	

Dosage Forms

The antibacterial agents of this invention can be administered by any means that produces contact of the active agent with the agents' site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and the effect desired. Usually, a daily dosage of active ingredient can be about 5 to 20 milligrams per kilogram of body weight. Ordinarily, when the more potent compounds of this invention are used, 5 to 15, and preferably 5 to 7.5 milligrams per kilogram per day, given in divided oral doses 2 to 4 times a day or in sustained release form, is effective to obtain desired results. These drugs may also be administered parenterally.

Projected therapeutic levels in humans should be attained by the oral administration of 5-20 mg/kg of body weight given in divided doses two to four times daily. The dosages may be increased in severe or life-threatening infections.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active

ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, manitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and, if necessary, buffer substances. Antiooxidants such as sodium bisulfate, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 75 milligrams of powdered active ingredient, 150 milligrams of lactose, 24 milligrams of talc, and 6 mlligrams of magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 75 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 75 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 250 milligrams for microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectables

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspensions

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 75 milligrams of finely-divided active ingredients. 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

Utility

Test results indicate that the novel compounds of this invention are biologically active against gram positive bacteria including multiply antibiotic resistant strains of staphylococci and streptococci. These compounds are potentially useful for the treatment of both human and animal bacterial infections including diseases of the respiratory, gastrointestinal, genitoturinary systems; blood; interstitial fluids; and soft tissues.

As shown in Table IV, compounds of Formula (I) exert an in vitro antibacterial effect. A standard microdilution method (National Committee for Clinical Standards. Tentative standard M7-T. Standard methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Villanova, PA. 1982) with Mueller-Hinton broth is used to determine the 24-hour minimal inhibitory concentrations (MIC's) for test strains of Staphylococcus aureus and Escherichia coli.

The in vivo potency of these compounds is exemplified by the data summarized in Table V. Determinations of in vivo efficacy are performed by inoculating mice intraperitoneally with cultures of the infecting organism diluted to produce 100% mortality in control animals within twenty-four hours. The culture of S. aureus used to infect the animals was diluted to the required bacterial density using 5% aqueous hog gastric mucin. The compounds are dissolved or suspended in 0.25% aqueous Methocel® (Methocel®: Hydroxypropyl Methylcellulose, E15 Premium, Dow Chemical Company) for oral administration or sterile distilled water containing 5% dimethylsulfoxide (Fisher Scientific Company, Fairlawn, NJ) for subcutaneous administration. The mice are dosed at one hour and at four hours post-infection. Mortality is recorded daily until test termination seven days post infection. The number of survivors in each treatment group on the seventh day after infection is used in the calculation of the ED_{50}, the dose of compound that protects 50% of the mice (Litchfield, J. T. and Wildoxon. A simplified method for evaluating dose-effect experiments. J. Pharmacol Exp. Ther., 96:99-113, 1949).

Table IV

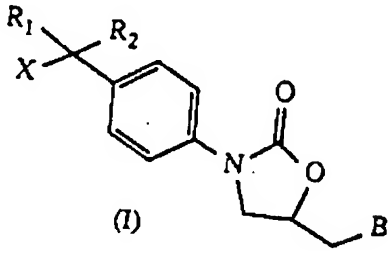
In Vitro Broth Microdilution Minimal Inhibitory Concentrations (MIC's)		
Ex. No.	Minimum Inhibitory Concentration (μg/mL)	
	Staphylococcus aureus	Escherichia coli
1	4	>128
2	4	>128
3	4	>128
5	8	>128
6	1	>128
7	32	>128
8	4	>128
9	1	>128
10	16	>128
11	4	>128
15	8	>128
20	32	>128

Table V

In Vivo Activity of Compounds Against Staphylococcus Aureus in an Acute Lethal Mouse Model		
Ex. No.	ED_{50} (mg/kg)	
	Oral Administration	Subcutaneous Administration
1	40	20
2	47	60
3	41	15
5	42	25
6	30	26
7	>120	>120
8	>90	>90
9	>90	>90
10	>90	>90
11	>90	>90
15	>90	59
20	65	52

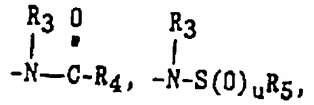
Claims

1. A compound having the formula:

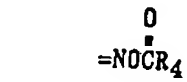


(I)

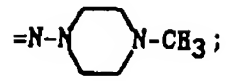
wherein for the t isomer or racemic mixtures containing it
B is NH_2,



or N_3
u is 1 or 2;
R_3 is H, alkyl of 1-10 carbon atoms, or cycloalkyl of 3-8 carbon atoms;
R_4 is H, alkyl of 1-4 carbon atoms, alkenyl of 2-4 carbon atoms, cycloalkyl of 3-4 carbon atoms, or OR_5;
R_5 is alkyl of 1-4 carbon atoms;
R_1 and R_2 taken together are H_2, H and OH, =O, =NOH, H and $N(R_6)_2$, $=NOR_5$,

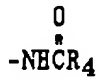


or



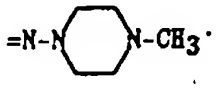
R_6 is H or alkyl of 1-4 carbon atoms;
X is pyridinyl or phenyl optionally substituted with from 1-3 substituents each independently selected from a group selected from halogen, alkyl of 1-4 carbon atoms, NO_2, OR_5, or $S(O)_mR_5$; and
m is 0, 1 or 2;
or a pharmaceutically suitable salt thereof.

2. A compound of Claim 1 wherein B is



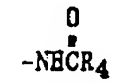
where R_4 is H, CH_3, or OR_5.

3. A compound of Claim 1 wherein R_1 and R_2 taken together are H_2, H and OH, =O, =NOH, or

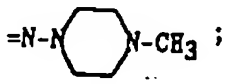


4. A compound of Claim 1 wherein X is 3-pyridinyl or phenyl optionally substituted with 1-2 substituents each independently selected from halogen, NO_2, $S(o)_mR_5$, or OR_5.

5. A compound of Claim 1 wherein:
(a) B is



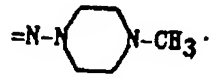
where R_4 is H, CH_3, or OR_5;
(b) R_1 and R_2 taken together are H_2, H and OH, =O, =NOH, or



and
(c) X is 3-pyridinyl or phenyl optionally substituted with 1-2 substituents each independently selected from halogen, NO_2, $S(O)_mR_5$, or OR_5.

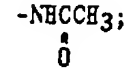
6. A compound of Claim 1 wherein B is

7. A compound of Claim 1 wherein R_1 and R_2 taken together are H_2, H and OH, =O, or

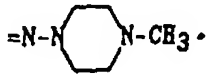


8. A compound of Claim 1 wherein X is phenyl optionally substituted with from 1-2 substituents each selected from F, Cl, NO_2, or OCH_3.

9. A compound of Claim 1 wherein:
(a) B is



(b) R_1 and R_2 taken together are H_2, H and OH, =O, or

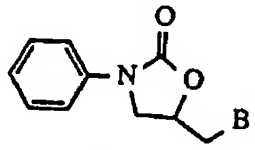


(c) X is phenyl optionally substituted with from 1-2 substituents each selected from F, Cl, NO_2, or OCH_3.

10. Compounds of Claim 1 selected from (ℓ)-N-[3-[4-(2,4-difluorobenzoyl)phenyl]-2-oxo-oxazolidin-5-ylmethyl]acetamide; (ℓ)-N-[3-[4-(4-nitrobenzoyl)phenyl]-2-oxooxazo-lidin-5-ylmethyl]acetamide; and (ℓ)-N-[3-[4-(4-fluorobenzoyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

11. A pharmaceutical composition consisting essentially of a pharmaceutically suitable carrier and an antibacterial amount of a compound of any of Claims 1 to 10.

12. A process for preparing a compound of Claim 1 which comprises:
(a) when R_1 and R_2 taken together are =O, contacting a compound of the formula:

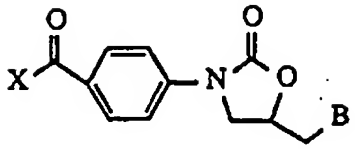


(II)

where B is defined in Claim 1 with a carboxylic acid of the formula

XCO_2H

where X is defined in Claim 1 in the presence of a mixture of methanesulfonic acid, and methanesulfonic anhydride, or a mixture of trifluoromethanesulfonic acid and trifluoromethane sulfonic anhydride to prepare a compound of the formula:



(III)

and

(b) when R_1 and R_2 taken together are as defined in Claim 1 other than =O, contacting a compound of Formula (III) prepared in step (a) with:

(i) hydrogen gas in the presence of a hydrogenation catalyst; or

(ii) an alkali metal borohydride; or

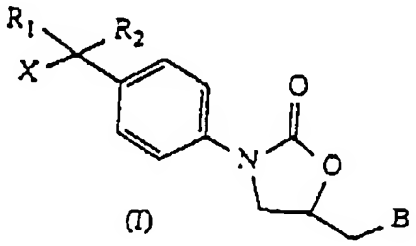
(iii) $(R_5)_2NH$ in the presence of sodium cyanoborohydride; or

(iv) H_2NOH or H_2NOR_5 in the presence of a base; or

(v) 1-amino-4-methylpiperazine in a refluxing solvent.

Revendications

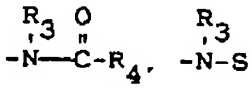
1. Un composé présentant la formule:



(I)

dans laquelle, pour l'isomère *l* ou les mélanges racémiques le contenant:

B est NH_2,



$(O)_uR_6$ ou N_3, ou

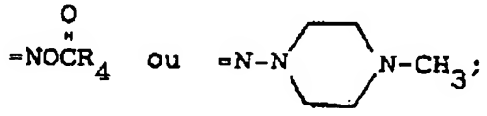
u vaut 1 ou 2;

R_3 est H ou un radical alkyle ayant 1 à 10 atomes de carbone ou cycloalkyle ayant 3 à 8 atomes de carbone;

R_4 est H ou un radical alkyle ayant 1 à 4 atomes de carbone, alkényle ayant 2 à 4 atomes de carbone, cycloalkyle ayant 3 à 4 atomes de carbone, OU OR_5;

R_5 est un radical alkyle ayant 1 à 4 atomes de carbone;

R_1 et R_2, pris ensemble, forment H_2, H et ON, =O, =NOH, H et $N(R_5)_2$, $=NOR_5$,



R_6 est H ou un radical alkyle ayant 1 à 4 atomes de carbone;

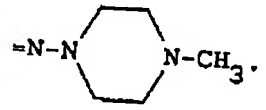
X est le radical pyridinyle ou un radical phényle éventuellement substitué par 1 à 3 substituants dont chacun est, indépendamment des autres, choisis parmi l'ensemble comprenant les halogènes, les radicaux alkyles ayant 1 à 4 atomes de carbone, NO_2, OR_5 ou $S(O)_mR_5$; et

m vaut O, 1 ou 2;

ou un de ses sels pharmaceutiquement acceptables.

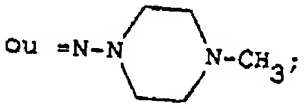
2. Un composé selon la revendication 1, dans lequel B est $-NHC(O)R_4$ où R_4 est H, CH_3 ou OR_5.

3. Un composé selon la revendication 1, dans lequel R_1 et R_2, pris ensemble, forment H_2, H et OH, =O, =NOH ou



4. Un Composé selon la revendication 1, dans lequel X est le radical 3-pyridinyle ou un radical phényle éventuellement substitué par 1 ou 2 substituants qui, indépendamment l'un de l'autre, sont chacun choisis parmi les halogènes, NO_2, $S(O)_mR_5$ ou OR_5.

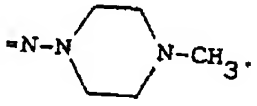
5. Un composé selon la revendication 1, dans lequel:
(a) B est $-NHC(O)R_4$ où R_4 est H, CH_3 ou OR_5;
(b) R_1 et R_2, pris ensemble, forment H_2, H et OH, =O, =NOH



et
(c) X est le radical 3-pyridinyle ou un radical phényle éventuellement substitué par 1 ou 2 substituants qui, indépendamment l'un de l'autre, sont choisis parmi les halogènes, NO_2, $S(O)_mR_5$ ou OR_5.

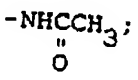
6. Un composé selon la revendication 1, dans lequel B est $-NHC(O)CH_3$.

7. Un composé selon la revendication 1, dans lequel R_1 et R_2, pris ensemble, forment H_2, H et OH, =O ou

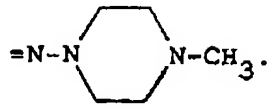


8. Un composé selon la revendication 1, dans lequel X est un radical phényle éventuellement substitué par 1 ou 2 substituants dont chacun est choisi parmi F, Cl, NO_2 ou OCH_3.

9. Un composé selon la revendication 1, dans lequel:
(a) B est



(b) R_1 et R_2, pris ensemble, forment H_2, H et OH, =O ou



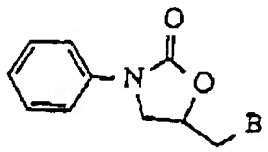
(c) X est un radical phényle éventuellement substitué par 1 ou 2 substituants dont chacun est choisi parmi F, Cl, NO_2 ou OCH_3.

10. Composés selon la revendication 1, choisis parmi le (ℓ)-N-[3-[4-(2,4-difluorobenzoyl)phényl]-2-oxo-oxazolidin-5-ylméthyl]acétamide; le (ℓ)-N-[3-[4-(4-nitrobenzoyl)phényl]-2-oxo-oxazolidine-5-ylméthyl]-acétamide; le (ℓ)-N-[3-[4-(4-fluorobenzoyl)phényl]-2-oxo-oxazolidine-5-ylméthyl]acétamide.

11. Une composition pharmaceutique constituée essentiellement d'un support pharmaceutiquement approprié et d'une quantité à effet antibactérien d'un composé selon l'une quelconque des revendications 1 à 10.

12. Un procédé de préparation d'un composé selon la revendication 1, qui consiste:

(a) quand R_1 et R_2, pris ensemble, forment =O, à mettre en contact un composé de formule:

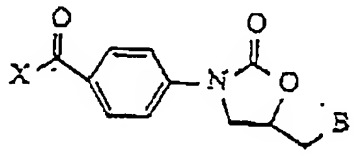


(II)

dans laquelle B est tel que défini dans la revendication 1,
avec un acide carboxylique de formule:

XCO_2H

dans laquelle X est tel que défini dans la revendication 1,
en présence d'un mélange d'acide méthanesulfonique et d'anhydride méthanesulfonique, ou d'un mélange d'acide trifluorométhanesulfonique et d'anhydride trifluorométhanesulfonique, pour préparer un composé de formule:



(III)

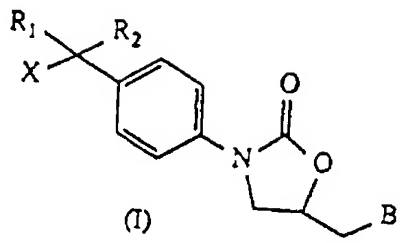
et

(b) quand R_1 et R_2, pris ensemble, sont tels que définis dans la revendication 1 et sont autres que =O, à mettre en contact un composé de formule (III) préparé dans l'étape (a) avec:

(i) de l'hydrogène gazeux en présence d'un catalyseur d'hydrogénation; ou
(ii) un borohydrure de métal alcalin; ou
(iii) du $(R_5)_2NH$ en présence de cyanoborohydrure de sodium; ou
(iv) du H_2NOH ou H_2NOR_5 en présence d'une base; ou
(v) de la 1-amino-4-méthylpipérazine dans un solvant au reflux.

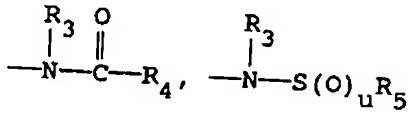
Patentansprüche

1. Verbindung der Formel

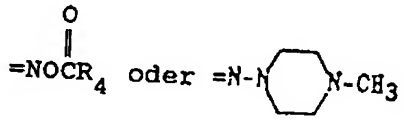


(I)

worin
für das ℓ-Isomer oder dieses enthaltende racemische Gemische
B NH_2,

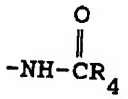


oder N_3 ist;
u 1 oder 2 ist;
R_3 H, Alkyl mit 1 bis 10 Kohlenstoff-Atomen oder Cycloalkyl mit 3 bis 8 Kohlenstoff-Atomen ist;
R_4 H, Alkyl mit 1 bis 4 Kohlenstoff-Atomen, Alkenyl mit 2 bis 4 Kohlenstoff-Atomen, Cycloalkyl mit 3 bis 4 Kohlenstoff-Atomen oder OR_5 ist;
R_5 Alkyl mit 1 bis 4 Kohlenstoff-Atomen ist;
R_1 und R_2 zusammengenommen H_2, H und OH, =O, =NOH, H und $N(R_6)_2$, $=NOR_5$,



sind;
R_6 H oder Alkyl mit 1 bis 4 Kohlenstoff-Atomen ist;
X Pyridinyl oder Phenyl ist, das gegebenenfalls mit 1 bis 3 Substituenten substituiert ist, die unabhängig voneinander aus einer aus Halogen, Alkyl mit 1 bis 4 Kohlenstoff-Atomen, NO_2, OR_5 oder $S(O)_mR_6$ bestehenden Gruppe ausgewählt sind; und
m 0, 1 oder 2 ist;
oder ein pharmazeutisch geeignetes Salz derselben.

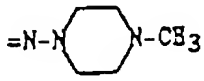
2. Verbindung nach Anspruch 1, worin

B 

ist, worin

R_4 H, CH_3 oder OR_5 ist.

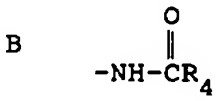
3. Verbindung nach Anspruch 1, worin
R_1 und R_2 zusammengenommen H_2, H und OH, =O, =NOH oder



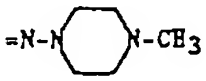
sind.

4. Verbindung nach Anspruch 1, worin X 3-Pyridinyl oder Phenyl ist, das gegebenenfalls mit 1 bis 2 Substituenten substituiert ist, die unabhängig voneinander aus Halogen, NO_2, $S(O)_mR_6$ oder OR_5 ausgewählt sind.

5. Verbindung nach Anspruch 1, worin
(a)

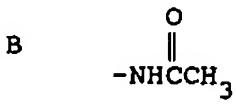


ist, worin R_4 H, CH_3 oder OR_5 ist;
(b) R_1 und R_2 zusammengenommen H_2, H und OH, =O, =NOH oder



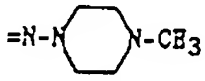
sind; und
(c) X 3-Pyridinyl oder Phenyl ist, das gegebenenfalls mit 1 bis 2 Substituenten substituiert ist, die unabhängig voneinander aus Halogen, NO_2, $S(O)_mR_5$ oder OR_5 ausgewählt sind.

6. Verbindung nach Anspruch 1, worin



ist.

7. Verbindung nach Anspruch 1, worin
R_1 und R_2 zusammengenommen H_2, H und OH, =O oder

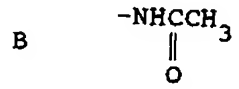


sind.

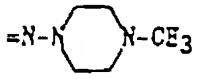
8. Verbindung nach Anspruch 1, worin
X Phenyl ist, das gegebenenfalls mit 1 bis 2 Substituenten substituiert ist, die unabhängig

voneinander aus F, Cl, NO_2 oder OCH_3 ausgewählt sind.

9. Verbindung nach Anspruch 1, worin
(a)



ist.
(b) R_1 und R_2 zusammengenommen H_2, H und OH, =O oder

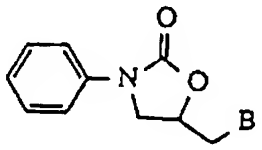


sind;
(c)
X Phenyl ist, das gegebenenfalls mit 1 bis 2 Substituenten substituiert ist, die unabhängig voneinander aus F, Cl, NO_2 oder OCH_3 ausgewählt sind.

10. Verbindungen nach Anspruch 1, ausgewählt aus (ℓ)-N-[3-[4-(2,4-Difluorbenzoyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamid; (ℓ)-N-[3-[4-(4-Nitrobenzoyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamid; und (ℓ)-N-[3-[4-(4-Fluorbenzoyl)phenyl]-2-oxooxazolidin-5-ylmethyl]acetamid.

11. Pharmazeutische Zusammensetzung, bestehend im wesentlichen aus einem pharmazeutisch geeigneten Träger und einer antibakteriellen Menge einer Verbindung nach irgendeinem der Ansprüche 1 bis 10.

12. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, umfassend:
(a) wenn R_1 und R_2 zusammengenommen =O sind, das InBerührung-Bringen einer Verbindung der Formel

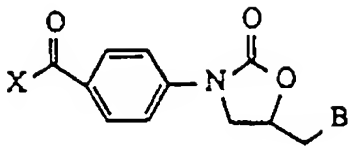


(II)

in der B die in Anspruch 1 angegebenen Bedeutungen hat, mit einer Carbonsäure der Formel

XCO_2H

in der X die in Anspruch 1 angegebenen Bedeutungen hat,
in Gegenwart eines Gemischs aus Methansulfonsäure und Methansulfonsäureanhydrid oder eines Gemischs aus Trifluormethansulfonsäure und Trifluormethansulfonsäureanhydrid, um eine Verbindung der Formel



(III)

herzustellen; und

(b) wenn R_1 und R_2 zusammengenommen gemäß der Definition in Anspruch 1 nicht =O sind, das In-Berührung-Bringen einer in Schritt (a) hergestellten Verbindung der Formel (III) mit

(i) Wasserstoff-Gas in Gegenwart eines Hydrierungs-Katalysators; oder

(ii) einem Alkalimetallborhydrid; oder

(iii) $(R_5)_2NH$ in Gegenwart von Natriumcyanborhydrid; oder

(iv) H_2NOH oder H_2NOR_5 in Gegenwart einer Base; oder

(v) 1-Amino-4-methylpiperazin in einem zum Rückfluß erhitzten Lösungsmittel.